Overview of Cross-company CMC Discussions Related to COVID-19 Vaccines

Parenteral Drug Association

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2022 PDA Asia Pacific Regulatory Conference

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VE/ IFPMA CMC COVID Task Force

Vaccines Europe (VE)

- T Gastineau (Sanofi) - lead
- D Wilkinson (AZ) *& COVAX Manufacturing SWAT VE representative*
- C Campa (GSK)
- K Cappio (Novavax)
- A Czwarno (VE)
- N Dubois (Pfizer)
- S Meillerais (MSD)
- R Nachbagauer (Moderna)
- F Neske (Curevac)
- D Steenvoorden (Janssen)
- BQ Truong (Sanofi)
- M van Ooij (Janssen)
- F Wauters (MSD)
- R Youil (Seqirus)

International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

- M McGoldrick (MSD) *& COVAX Manufacturing SWAT IFPMA representative*
- P Barbosa (IFPMA)

Background

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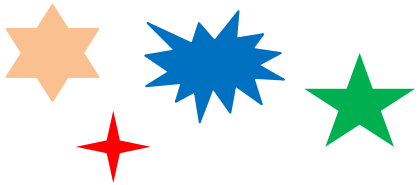
Vaccine Products

Antigen(s)



- Needed for **specificity of the immune response**
- Depending on the vaccine platform, may be **directly administered** (e.g., subunit vaccines, inactivated or live attenuated vaccines) **or generated in the body after administration** (e.g., mRNA and viral vector vaccines)
- **Complex and multiple antigens** (with different structural features and doses) **may be combined** (e.g., some glycoconjugate/ protein subunit vaccines)

Adjuvants & delivery vehicles

- Depending on the vaccine platform, **adjuvants or delivery vehicles** may be needed.
  - **Aluminum salts or Adjuvant Systems** (combination of immunostimulatory molecules) may be a component. Needed **for most of the inactivated (whole or subunit) vaccines to enhance and modulate immunogenicity of the vaccine antigen**
  - **Delivery vehicles (e.g., lipid nanoparticles, LNPs)** are needed for mRNA vaccines to increase stability and ensure adsorption and fusion with the cell membrane

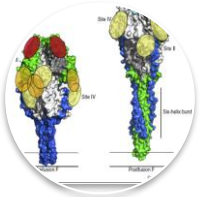
Administered Vaccine

- All components in an **appropriate formulation**
- **May require reconstitution/ mixing of different component** before administration
- **Typically filled in vial or syringe, but other administration routes are/ will be possible** depending on the product characteristics and medical need (e.g., oral solutions, microneedles, inhalation)

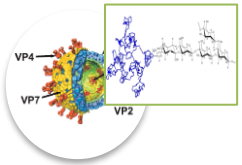
Yingzhu Li, Rumiana Tenchov, Jeffrey Smoot, Cynthia Liu, Steven Watkins, and Qiongqiong Zhou, *ACS Central Science* **2021** 7 (4), 512-533
DOI: 10.1021/acscentsci.1c00120

Carmine D'Amico · Flavia Fontana, Ruoyu Cheng, Hélder A. Santos, *Drug Delivery and Translational Research* (2021) 11:353–372
https://doi.org/10.1007/s13346-021-00924-7

Challenges for acceleration of Biologics development

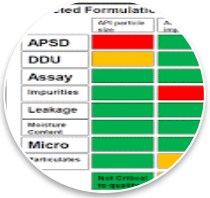


Complex products and processes → quality attributes monitoring & assessment of impact of process on quality



Wide variety of possible product ***categories/ structural*** features, → sometimes limited possibility to leverage information from different products

Analytical strategy: structural and formulation changes → impact on efficacy



Knowledge of **antigen structure, formulation, analytics and process** are instrumental for quality attributes and ranges to be (clinically) explored as needed

Aggressive timelines : product, process, analytical development (especially in case of disease outbreaks and pandemics)

Areas of concern & opportunities for acceleration, beyond development

Development

- Early product understanding (QbD)
- CMC risk assessment to identify priorities (QbD)
- Prior Knowledge
- New technologies/ modeling strategies

Registration

- Early engagement with regulators
- Build lifecycle plans
- Harmonization/ reliance across regions

Post- approval supply

- Continued assessment of new knowledge, technologies, modeling strategies
- Post- Approval Change Management
- Harmonization/ reliance across regions
- (Global) supply

Cross- company discussions and dialogue with Regulators

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Cross- company positions and dialogue with Regulators

CMC Acceleration for unmet medical need

EMA PRIOR KNOWLEDGE WORKSHOP
Prior Knowledge

EFPIA unmet medical need paper
EFPIA 2017 unmet med. nee

EMA/FDA PRIME workshop 2018
PRIME/BT

VE stability modelling paper
https://www.mdpi.com/2076-393X/9/10/1114
Vaccines **2021**, *9*, 1114.

EMA Toolbox
EMA Toolbox

CMC Acceleration to address COVID & future pandemics

EFPIA COVID CMC elements, EFPIA 2020 COVID CMC
The AAPS journal. Volume 24. 6. Pages 101
Industry position on manufacturing capacity, IFPMA COVID

2021 ICMRA workshop
ICMRA Report

2022 Vaccines COVID
- Overarching proposals [1]
- Lessons learned & tech. refl. [2]

COVAX workshops
https://epi.tghn.org/covax-overview/manufacturing

WHO technical briefs, e.g.
(https://cdn.who.int/media/docs/default-source/medicines/regulatory-updates/covid-19/tech-brief_regulation-of-covid-19-vaccines_synopsis_aug2020_feb2021_v14apr2021.pdf?sfvrsn=70fecf6d_5&download=true)

1) Vaccine 40 (2022) 1215–1222
2) Vaccine 40 (2022) 1223–1230

Benefit/risk ratio changes from acceleration to pandemic, but similar acceleration enablers

Several routine CMC requirements and challenges could be "barriers" to timely & equitable supply of COVID-19 vaccines

- Process validation
- Comparability
- Stability
- Post Approval Changes
- Release testing by HAs
- Packaging & Labeling
- GMOs
- Strain changes

Not all data available at time of initial authorization

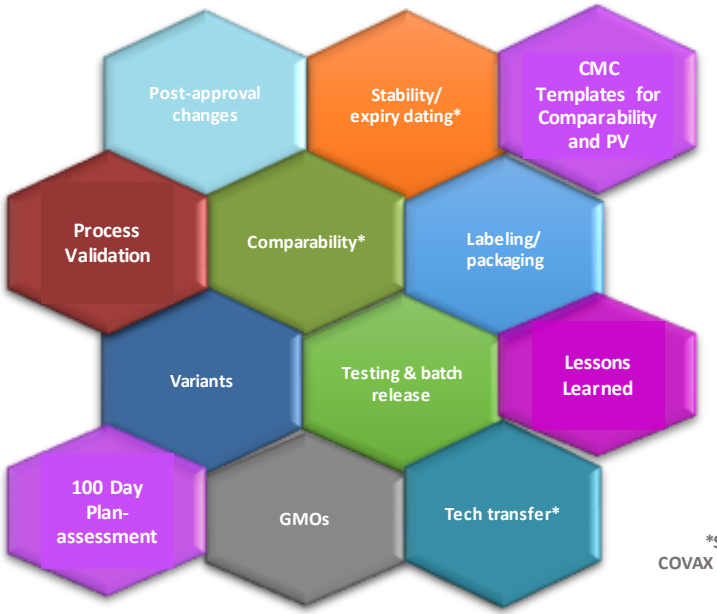
Lot (20 – 100) of PACs to be managed within weeks / few months after initial authorization in all countries

Multiple redundant activities

Lack of harmonization in requirements and processes

Long regulatory processes

Focus on COVID Vaccines: The CMC COVID task force (VE & IFPMA)



*Support to COVAX workshop

- **WHO** FAQ (https://www.who.int/publications/m/item/frequently-asked-questions-on-regulation-of-covid-19-vaccines)
- **WHO** Technical Brief: Regulation of COVID-19 Vaccines Synopsis from the August to February 2021 COVAX RAG meetings (https://cdn.who.int/media/docs/default-source/medicines/regulatory-updates/covid-19/tech-brief_regulation-of-covid-19-vaccines_synopsis_aug2020_feb2021_v14apr2021.pdf?sfvrsn=70fecf6d_5&download=true)
- **WHO** Technical Brief: Regulation of COVID-19 Vaccines Synopsis from the April 2021 COVAX RAG meetings https://media.tghn.org/medialibrary/2021/05/Tech_Brief_Regulation_of_COVID-19_vaccines_Synopsis_May_2021.pdf
- **WHO** considerations for the assessment of COVID-19 vaccines https://www.who.int/publications/m/item/considerations-for-the-assessment-of-covid-19-vaccines-for-listing-by-who

9 Position papers issued and communicated to Manufacturing SWAT/ COVAX RAG (status as of February 2022); newer initiatives in purple

Note: see https://epi.tghn.org/covax-overview/manufacturing/ for the list of COVAX workshops (including minutes and presentations)

COVAX- the vaccines pillar of the ACT Accelerator, launched by CEPI, Gavi, and WHO

Enabling Sciences

The Enabling Sciences SWAT team provides cross-cutting support to COVID-19 vaccine developers in the area of diagnostics, standards, assays and animal models.

Clinical Development and Operations

The Clinical Development and Operations SWAT team collaborates on initiatives related to clinical operations, vaccine safety, vaccine science and maternal immunization.

Manufacturing

The Manufacturing SWAT team provides cross-cutting support to COVID-19 vaccine developers in the area of Drug Substance (DS) and Drug Product (DP) scale-up and scale-out, supply chain and release assays.

Regulatory Advisory Group

The COVAX Regulatory Advisory Group works to address regulatory issues and challenges identified by the enabling sciences, clinical development and operations, and manufacturing SWAT teams.

CEPI, alongside Gavi and the World Health Organisation, launched COVAX – the vaccines pillar of the ACT Accelerator – with the aim of ending the acute phase of the pandemic by the end of 2021.

From:
https://epi.tghn.org/covax-overview/

Leveraging those opportunities would help to overcome all "barriers"

	Science & Risk-based	Convergence & Harmonization	Reg Reliance	Digital
Process validation	✓	✓	✓	✓
Comparability	✓	✓	✓	✓
Stability	✓	✓	✓	✓
Post Approval Changes	✓	✓	✓	✓
Release testing by HAs	✓	✓	✓	✓
Packaging & Labeling		✓	✓	✓
GMOs		✓	✓	
Strain changes	✓	✓	✓	

Science and risk- based approaches to support acceleration

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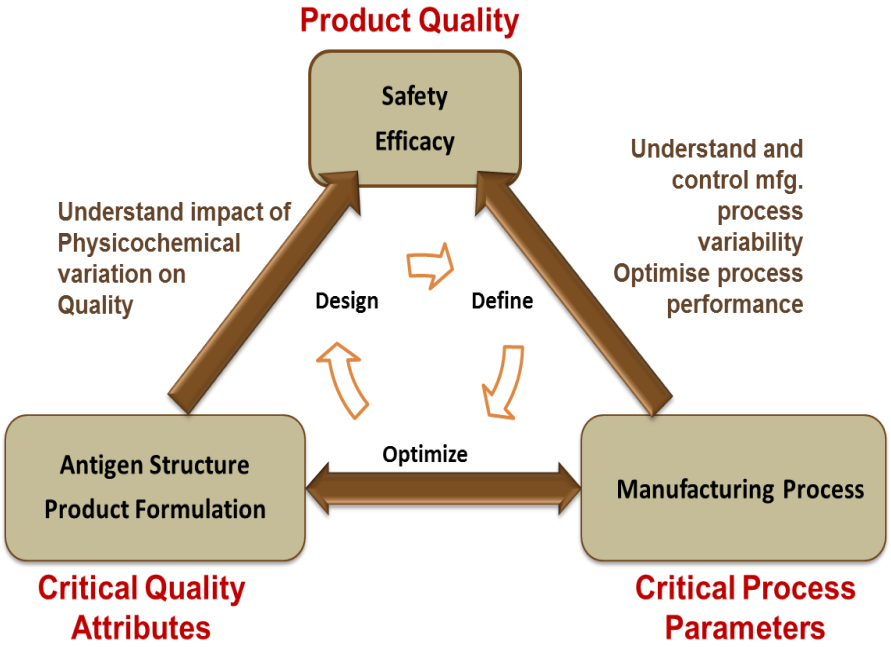
CMC and accelerated supply for global access

- Keeping pace for CMC is enabled by early rigorous definition of the drug's attributes affecting its product quality (safety and efficacy)

- This knowledge allows for flexibility in process development, and acceptability of process and scale change throughout clinical development and final commercial manufacturing

- The foundational principles of **Quality-by-Design** drive us to understand what is critically important for product quality taking a patient-centric view, and to design the product and its manufacturing processes to ensure this in the fastest, and most efficient manner possible.

Quality by Design (QbD), vaccine example



Quality by Design—An Indispensable Approach to Accelerate Biopharmaceutical Product Development. (2021) Khan, M. A; Campa, C, Eds. PDA: Bethesda, Md., 2021.

How to go faster & ensure a sustainable supply?

faster

Acceleration

slower

- Push for early and deep product understanding
- Smart dose selection
- Comparability and reference standard strategy
- Innovation and (vs) prior knowledge

Specification attributes based on CQA identification, driving tailored structural characterization strategy

Process optimization may be deferred → changes supported by product understanding

"Process is product"

Focus on manufacturing consistency during development , used to set specifications

Untailored extensive product and process characterization without fully understanding the link vs activity

Speed to patient

Quality by Design—An Indispensable Approach to Accelerate Biopharmaceutical Product Development. (2021) Khan, M. A; Campa, C, Eds. PDA: Bethesda, Md., 2021.

"Patient-centric" approach: why is it so relevant in accelerated & emergency scenarios

- According to current cross-industry discussions, **patient-centric specifications** are "a **set of tests and acceptance ranges to which product quality attributes should conform for the product to be safe and effective when used as labeled. Justifications for acceptance ranges focus on risk-based assessment of the impact to patients**. Patient-Centric Specifications may also be referred to as clinically relevant specifications"*

- Clinically relevant specifications are important to support acceleration. Some of the reasons are reported below:

  •There is a **too limited number of lots** to support statistically driven acceptance criteria, or there is a larger amount of uncertainty when the sample size is low, especially when limited platform/ prior knowledge is available

  •**When product CQAs are understood, process optimization activities may be deferred-** manufacturing flexibility can be supported by acceptance criteria set with link to product attributes relevant for the patient, also supporting comparability assessment and lifecycle plans, if process improvements are also planned after launch

  •Especially in health emergency scenarios, it is important to **avoid to waste good lots due to over-restrictive specs limits set with limited/ not fully representative batches**, see for instance COVAX RAG reflections on COVID vaccines: (*https://www.who.int/publications/m/item/annex-1st-technical-brief-regulation-of-covid-19-vaccines*)

*M.N. Ruesch et al. / Journal of Pharmaceutical Sciences 110 (2021) 771-784

"Patient-centric" approach: how to ensure link to specifications

The link of specifications to product knowledge and impact on safety/ efficacy can be achieved through:

1. **Selection of the quality attributes** that are relevant to the patient (CQAs), based on the Quality Target Product Profile and analytical characterization/ structure-function understanding
2. **Identification** of scientifically sound **acceptance criteria**
3. **Integration of specification within the overall control strategy**, to select the relevant CQAs for routine test vs in-process or skip testing (e.g. for some impurities based on demonstrated and consistent low amount, well below safety limits) or to support range definition based on how representative the CQA range can be in development vs expected commercial product

Similar thinking can be applied to **Comparability strategies**, which are highly relevant in accelerated scenarios

Comparability- why is it so relevant and opportunities in COVID emergency scenario

- **Risk- based** comparability approaches, e.g., focusing on the CQAs impacted by the change*, **
- Target comparability on **product quality** vs process consistency, especially **where prior knowledge is limited and/ or in the absence of statistically based acceptance criteria (few lots)***, **
- Ensure proper **analytical characterization** and define **robust comparison** strategy in case of method changes* (reference standard and focus on method performances expectations**)
- Global use of general/broader Post- Approval Change Management Protocols **(PACMPs) for routine changes**
- The use of **release, forced degradation and/or characterization** data to support comparability demonstration

* https://www.who.int/publications/m/item/annex-1st-technical-brief-regulation-of-covid-19-vaccines
** https://media.tghn.org/medialibrary/2021/02/012720_Tech_transfer_workshop.pdf

Relevance of Comparability to support risk- based approaches for Process Validation

Questions

Can all relevant NRAs **recognize risk (based on ICH Q9) for defining the appropriate levels of validation for equipment, process and analytical methods** at time of submission, applying thinking in terms of benefit to patient, allowing companies to manage aspects within their PQS, or receiving data as post approval commitments, for example concurrent validation, with drug product validation being a post approval commitment as suggested in recent FDA guidance documents?

RAG reflection

Manufacturers should also agree with regulatory authorities on the **implementation plan for providing post-licensure data**.

Where multiple site manufacture and scale up was necessary […], **demonstration of comparability during development would help inform on the validation approach taken**. […].

It was recognized that analytical methods for batch release are not validated early in development, but **in the initial phase qualified methods could be considered acceptable together with qualified characterization tests**.

** Extract from https://www.who.int/publications/m/item/annex-1st-technical-brief-regulation-of-covid-19-vaccines*

Process Validation- why is it so relevant and opportunities in COVID emergency scenario

- **Process validation is commonly a critical path activity** for the commercial **application** and many **post approval** variations

- Risk associated with process validation could be alternatively **mitigated** through provision of protocols, the product control strategy, concurrent validation and/or continuous process verification, particularly where there is extensive prior and platform knowledge*; however, agreement of such approaches is often challenging to achieve**

- A risk-based approach to process validation, where data usually submitted at the time of license application could be deferred and submitted post-licensure, should be decided on a product/process specific basis and agreed with regulators before license submission. ***

- Such a decision would depend on platform knowledge, data to demonstrate that the process was under control, the history of compliance. ***

- Where multiple site manufacture and scale up was necessary, the RAG stressed that demonstration of comparability during development would help inform on the validation approach taken. ***

- Analytical methods for batch release are not validated early in development, but in the initial phase qualified methods could be considered acceptable together with qualified characterization tests *

- PPQ risk- based approaches could also be considered for variant vaccines ****

*https://www.ema.europa.eu/en/events/stakeholder-workshop-support-quality-development-early-access-approaches-such-prime-breakthrough
**https://www.efpia.eu/media/554681/cmc-development-manufacture-and-supply-of-covid-19-therapies-and-vaccines.pdf and references therein

***https://cdn.who.int/media/docs/default-source/medicines/regulatory-updates/covid-19/tech-brief_regulation-of-covid-19-vaccines_synopsis_aug2020_feb2021_v14apr2021.pdf?sfvrsn=70fecf6d_5&download=true
****https://media.tghn.org/medialibrary/2021/05/Tech_Brief_Regulation_of_COVID-19_vaccines_Synopsis_May_2021.pdf

The CEPI CMC platform protocol templates initiative

Objective

Build CMC platform protocol templates that are "pre-approved"/pre-agreed by worldwide regulators

- Ready-to-use tool based on agreed baseline and understanding
- Two areas: 1) comparability and 2) manufacturing process validation/PPQ
- Use for vaccine products in pandemic/emergency situations
- Keyword is PLATFORM – prior knowledge
- Content will build on COVID-19 lessons and other scientific and regulatory tools
- Templates to be
  - Disease-agnostic
  - Product-agnostic
  - Publicly available, i.e. "open source"

Concluding remarks

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Technical and Regulatory framework

What is going well	Some Gaps/ Opportunities
• Proactive Industry alignment (**cross- modality and cross- trade associations**) • **Position papers** covering several CMC topics, supporting COVAX and dialogue with WHO/NGOs/ Regulators (RAG) • Support broad **communication on CMC expectations & opportunities** to several vaccine developers (e.g. through COVAX, publications) • Several **CMC options discussed during EMA/ FDA early access workshop (2018)** have been considered to support emergency (and reflected in the "EMA Toolbox") • ICMRA/ industry workshop* • ICDRA**	• Need for **accelerated approvals and reliance on SRA or WHO PQ** • Fostering alignment on data requirements and timings for **Post- Approval Changes** • Dialogue across NCLs/ establishment of a global mechanism for **mutual recognition of NCLs testing** • Proactively start reflection on **post- emergency scenario** –what should still be appropriate in accelerated scenarios for unmet medical need, and what should be generally accepted as the "new normal"? • Continuing to work with the SWAT and RAG teams to **address opportunities for the next pandemic and routine vaccines based on the lessons learned** - including support to CEPI protocol initiative (Comparability and PV)

* http://www.icmra.info/drupal/sites/default/files/2021-07/covid-19_manufacturing_capacity_ws_presentation.pdf
** https://www.who.int/teams/regulation-prequalification/regulation-and-safety/regulatory-convergence-networks/icdra/extraordinary-(virtual)-icdra---presentations

Acknowledgement

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CEPI Steering Committee of the CMC platform protocol templates initiative

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- Adrian Azhari (DCVMN)
- Cristiana Campa (VE/ IFPMA CMC COVID Task Force)
- ShouBai Chao (CanSinoBIO)
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- Diane Wilkinson (Vaccines Europe/EFPIA)

Thank You

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Study Funding / Sponsorship statement:
This work was sponsored by GlaxoSmithKline Biologicals SA
Cristiana Campa is a permanent employee of the GSK group of companies